American Journal of Medical Genetics 68:135–141 (1997)

Developmental Analysis of Cardiovascular System of 45,X Fetuses With Cystic Hygroma

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There have been few pathological investigations of 45,X embryos and fetuses from a developmental point of view. Since most 45,X embryos and fetuses are lost prenatally, it is important to investigate them morphologically in order to elucidate the pathogenesis of the abnormalities. In this study, 13 45,X fetuses with cervical cystic hygroma were examined between 12 and 23 weeks of pregnancy. Every case had a hypoplastic thymus. The aortic valve was bicuspid in 11 cases and unicuspid in 2 cases. The aortic arch showed tubular hypoplasia between the left carotid artery and the left subclavian artery in 12 cases and type B interruption in one case. Smooth muscle cells and elastic fibers were reduced in number in the hypoplastic aortic arch. These results suggest hypoplastic development of the fourth branchial arch. Combined abnormalities between the aortic arch and aortic valve are not infrequently observed in DiGeorge anomaly. A similar developmental mechanism apparently underlies the pathogenesis of 45,X embryos. Possible genes causing the abnormalities are discussed. Am. J. Med. Genet. 68:135–141, 1997 © 1997 Wiley-Liss, Inc.

KEY WORDS: 45,X, bicuspid aortic valve; tubular hypoplasia of the aortic arch; branchial arch; cystic hygroma

INTRODUCTION

Web neck has long attracted special attention in the Ullrich-Turner Syndrome (UTS). A possible developmental relationship between web neck and cervical cystic hygroma was suggested by Ullrich as early as 1938. Observations clearly demonstrated the intrauterine manifestation of cystic hygroma in aborted 45,X fetuses [Singh and Carr, 1966]. Web neck/cystic hygroma was statistically shown to be developmentally related to cardiovascular malformations in 45,X individuals [Clark, 1984].

A recent molecular genetic study demonstrated a candidate gene for the formation of UTS [Fisher et al., 1990]. However, few morphological investigations have focused on the essential pathogenesis of abnormalities of the syndrome. While most 45,X embryos and fetuses are lost during pregnancy [Hassold, 1986], it is important to examine them carefully from a developmental point of view.

In this study, the cardiovascular system of 45,X fetuses with cystic hygroma was studied to identify developmental characteristics. The results indicated an involvement of the aortic arch and valve as part of a developmental field defect.

MATERIALS AND METHODS

Thirteen 45,X fetuses with cervical cystic hygroma (Fig. 1A) were studied between 12 to 23 weeks of pregnancy (Table I). Four of the 13 cases (cases 1, 11, 12, and 13) were reported previously [Miyabara et al., 1989]. Multilocular cystic spaces were present in the hygroma of each fetus (Fig. 1B). There was also generalized edema, including puffing of the back of the hands and feet.

Chromosomes were analyzed from amniotic fluid (nine cases), chorionic villi of the placenta (three cases), or fetal blood cells (one case). Twelve fetuses were 45,X; one (case 8) was a mosaic 45,X/46,XX (50%:50%).

The cardiovascular system of each fetus was microdissected under a stereomicroscope. Each section was sketched by a camera lucida and photographed using a lens of Nikon's Medical Nikkor (Magnification X0.5-3), or Photomakroskop of Wild (M400, X2-10).

Smooth muscle cells of the aortic arch were immunohistochemically examined by a monoclonal anti-α-

Abbreviations: A, Ascending aorta; B, Brachiocephalic artery; C, Left common carotid artery; D, Ductus arteriosus; P, Pulmonary trunk; S, Left subclavian artery

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Received 29 June 1995; Accepted 17 May 1996

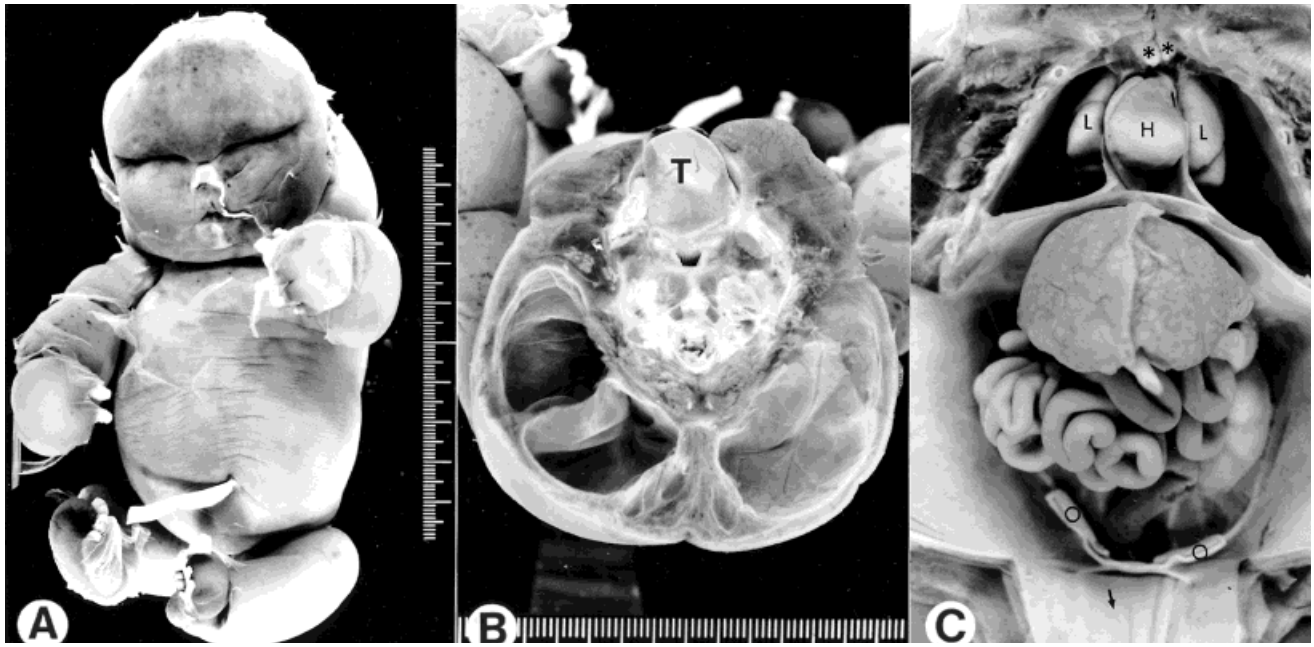

Fig. 1. Photomacrographs of a 45,X fetus (Case 11, 22 weeks). **A:** Fetus with maceration showing posterior cervical cystic hygroma, generalized edema, and cleft lip. **B:** Horizontal cut of the neck between the upper and lower jaw at the level of the tongue (T). Multilocular cystic spaces lined by a thin membrane are seen in the hygroma. **C:** Thoracic and abdominal cavities of the fetus. Thymus (*), heart (H), and lungs (L) are hypoplastic. Ovaries (O) and single umbilical artery (right side absence: arrow) are seen.

smooth muscle actin antibody (DAKO, M851). Elastic fibers were stained histochemically by Victoria blue alcohol solution.

RESULTS

The weight of all 45,X fetuses was heavier than that of normal Japanese fetuses at the same gestational age because of cystic hygroma and generalized edema. However, the crown-rump length of all 45,X fetuses did not greatly differ notably from that of normal Japanese fetuses between 12 to 23 weeks of pregnancy.

All 45,X fetus had a mildly to moderately hypoplastic thymus. The mediastinal soft tissue of the fetuses was obscured by the edema. Much fluid was present in the pericardial cavity of every 45,X fetus. The heart was hypoplastic (Fig. 1C). The right atrium and venae cavae were markedly dilated. The left superior vena cava, which drained into the right atrium through the dilated coronary sinus, persisted in five cases. In two cases, the right pulmonary vein was partially joined to the superior vena cava.

TABLE I. 45,X Fetuses With Cervical Cystic Hygroma

Cases	Age/C.-R./B.W.[a] (weeks/cm/g)	Chromosome
1	12/8.1/43	45,X
2	19/13.7/344	45,X
3	19/16.9/420	45,X
4	19/16.1/444	45,X
5	19/17.5/593	45,X
6	20/15.5/434	45,X
7	20/15.5/460	45,X
8	21/18.5/517	45,X/46,XX[b]
9	22/15.5/364	45,X
10	22/17.0/380	45,X
11	22/15.0/425	45,X
12	22/19.5/690	45,X
13	23/18.0/555	45,X

[a]B.W., body weight; C.-R., crown-rump length.
[b]45,X:46,XX = 50%:50%.

The ascending aorta was always hypoplastic compared to the descending aorta. In contrast, the pulmonary trunk and the ductus arteriosus were markedly dilated in every case (Fig. 2). The common outer surface around the ascending aorta and the pulmonary trunk was loosely expanded by many dilated small vessels including lymphatics (Fig. 3).

The aortic arch showed a uniform narrowing (tubular hypoplasia) particularly from the junction of the left common carotid artery to that of the ductus arteriosus in 12 of 13 cases (Table II, Figs. 2, 4A). In three of these cases (cases 2, 3, and 10), the arch was particularly narrow, consequently forming a slightly higher arch (Fig. 2, type E; Fig. 4B). One of the 13 cases (case 12) showed an interruption of the aortic arch after the branching of the left common carotid artery (type B interruption of the aortic arch) (Fig. 2, type F; Fig. 4C). The size of the aortic arch was smaller than that of the hypoplastic ascending aorta except in cases 1 and 7, in which the ascending aorta was markedly hypoplastic with a unicuspid aortic valve (Fig. 2, types A and B). In seven cases (cases 2, 3, 4, 6, 7, 10, and 11), the left subclavian artery branched off around the junction of the ductus arteriosus, consequently the isthmic part being absent (Fig. 2,

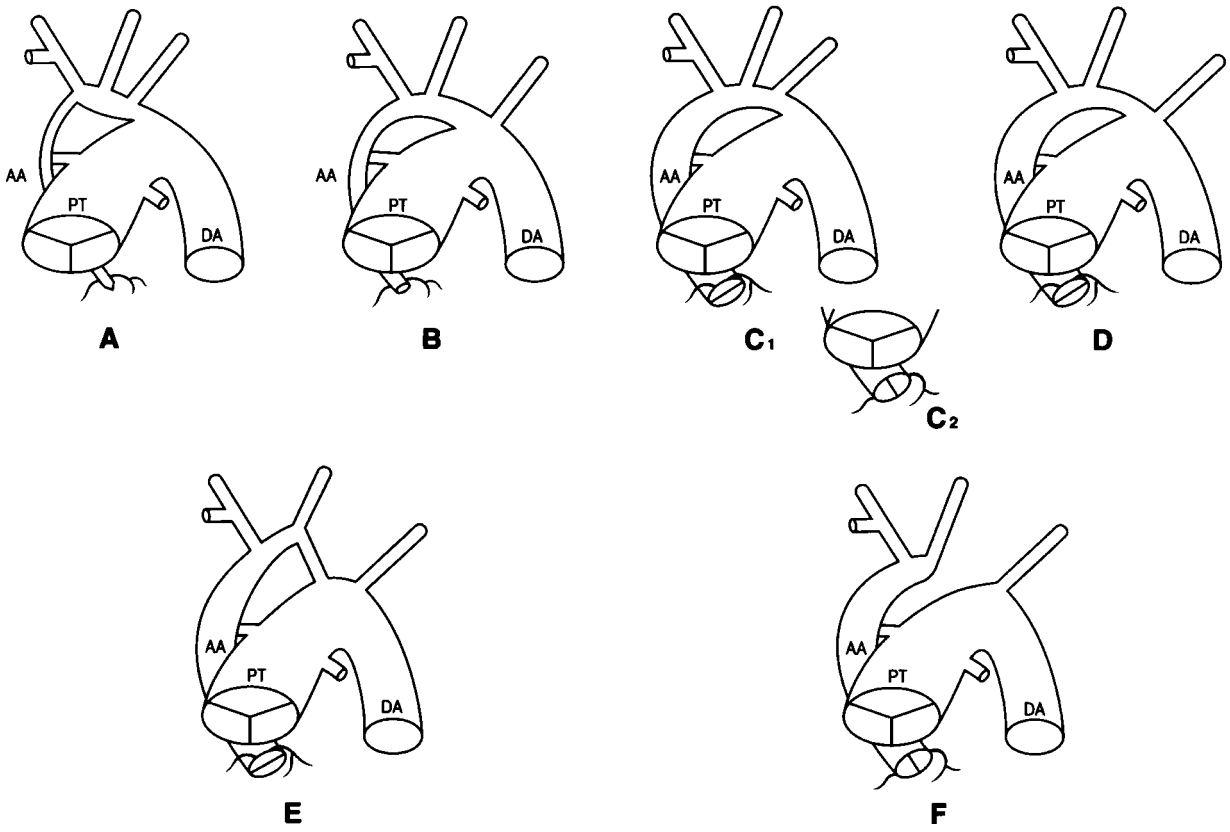

Fig. 2. Schematic illustration of different types of cardiovascular abnormalities in 45,X fetuses. **A,B:** Types with tubular hypoplasia of the aortic arch, markedly hypoplastic ascending aorta and unicuspid aortic valve. **C,D:** Types with tubular hypoplasia of the aortic arch and bicuspid aortic valve. **E:** A type with marked tubular hypoplasia of the aortic arch and bicuspid aortic valve. **F:** A type with interrupted aortic arch after branching of the left common carotid artery, and bicuspid aortic valve. AA, ascending aorta; DA, descending aorta; PT, pulmonary trunk.

types B, D, and E). The brachiocephalic artery and the left common carotid artery originated from a common trunk in the mosaic case (case 8, not shown).

Localized narrowing of the aortic arch was not detected in any of the cases by external observation; however, a circular prominence was observed inside the aortic arch just at the junction of the ductus arteriosus in two of four histologically examined cases.

The aortic valve was bicuspid in 11 of 13 cases (Table II). The semilunar valves were equal in size in most cases (Fig. 5A), while in a few cases they were unequal (Fig. 5B). The direction of the bicuspid aortic valve was either anteroposterior (8 cases, Fig. 2, types C_1, D, and E) or dextrosinistral (three cases, Fig. 2, types C_2 and F). In the remaining two cases having a markedly hypoplastic ascending aorta, there was only a valve-like tiny tissue in case 1 (Fig. 2, type A; Fig. 5C), and a valve-like tiny tissue and a small elevated tissue in case 7 (Fig. 2, type B) at the expected site of the semilunar valve. In the former, the outflow tract of the left ventricle showed atresia with calcification. The aortic valve of these two cases was interpreted as being unicuspid (Table II).

There were two ostia for the coronary arteries from the aorta in every case. Either both ostia were located on one cusp (eight cases, Fig. 2, types C_1, D, and E) or one ostium was located on each cusp (three cases, Fig. 2, types C_2 and F), except two cases had a unicuspid valve.

The left ventricular cavity was hypoplastic compared with the right cavity. In cases 1 and 7, which indicated a greatly hypoplastic ascending aorta, the left ventricular wall was concentrically thickened. The ventricular septum was intact in every case.

Histological examination of the aortic arch in 45,X fetuses showed that the thickness of the wall was less than one fourth that of a normal fetus. Smooth muscle cells detected by the anti-α-smooth muscle actin antibody, and elastic fibers stained by Victoria blue in the tunica media of the aortic arch were considerably decreased in number compared with those of a normal fetus (Fig. 6A,B).

Abnormal kidneys and single umbilical artery (Fig. 1C) were recognized in the extracardiac system (Table II).

DISCUSSION

Although tubular hypoplasia of the aortic arch in 45,X embryos and fetuses has occasionally been de-

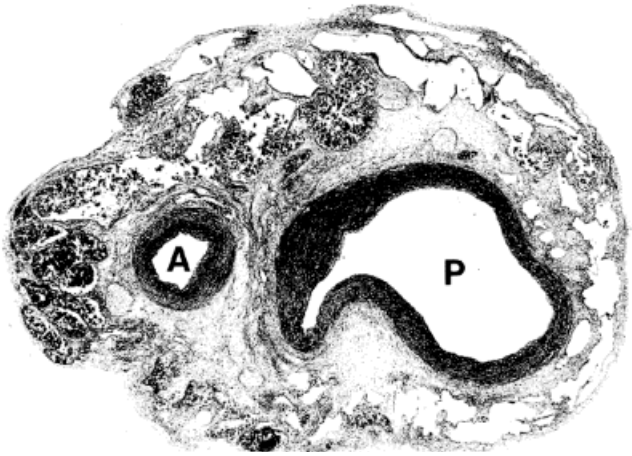

Fig. 3. Photomicrograph showing horizontal section of the ascending aorta and the pulmonary trunk in a 45,X fetus (case 7). Note markedly dilated veins as well as lymphatics not only around the ascending aorta but also around the pulmonary trunk, as well. Elastica Van Gieson staining, ×6.25.

scribed [Canki et al., 1988; Keeling, 1993], the present study clearly demonstrated that this characteristic is a typical cardiovascular malformation of 45,X fetuses with cystic hygroma. Such a uniform narrowing of the aortic arch, having been inappropriately described as coarctation in the previous study [Miyabara et al., 1989], would be more accurately termed tubular hypoplasia [Becker, 1972]. The hypoplasia was considered to exist essentially in the part of the aortic arch between the left common carotid artery and the left subclavian artery, since the isthmus was absent in 7 of 12 cases with tubular hypoplasia (Fig. 2, types B, D, and E). Type B interruption of the aortic arch in case 12 could be included in the same developmental spectrum with the tubular hypoplasia between the left common carotid artery and the left subclavian artery. This abnormality, therefore, differs slightly from that of UTS patients in whom coarctation of the aorta is recognized exclusively in the arch [Nora et al., 1970; Schinzel, 1983].

The hypoplastic or interrupted part of the aortic arch corresponds developmentally to the left 4th aortic arch [Van Mierop and Kutsche, 1984]. In contrast, abnormal origin of the right subclavian artery, which results from obliteration of the right 4th aortic arch, is only rarely reported in newborns with UTS [Van Egmond et al., 1988]. These facts suggest that the left 4th aortic arch is predominantly hypoplastic in 45,X embryos.

A bicuspid aortic valve is present in approximately half of the cases with coarctation of the aorta, which is frequently associated with tubular hypoplasia of the aortic arch [Becker, 1972]. In UTS, a bicuspid aortic valve is echocardiographically demonstrated more frequently than expected [Miller et al., 1983]. In the present study, a bicuspid aortic valve was observed in 11 cases and 2 cases showed a unicuspid aortic valve, indicating that

TABLE II. Abnormalities of 45,X Fetuses With Cystic Hygroma*

Case	Ao V	Ao arch	Type[a]	Other cardiovascular abnormalities	Extracardiac abnormalities
1	UC	Tubular	A	Closed foramen ovale, mitral stenosis, dysplastic tricuspid valve, aortic atresia, persistent left superior vena cava	Horseshoe kidney, single umbilical artery[b]
2	BC	Tubular	E	—	Open eyelids
3	BC	Tubular	E	Persistent left superior vena cava	—
4	BC	Tubular	D	Persistent left superior vena cava	High-arched palate
5	BC	Tubular	C_2	—	—
6	BC	Tubular	D	Persistent left superior vena cava	—
7	UC	Tubular	B	Persistent left superior vena cava, partial anomalous pulmonary venous drainage	Horseshoe kidney
8	BC	Tubular	C_2	Common brachiocephalic trunk	Accessory spleen
9	BC	Tubular	C_1	—	Renal dysplasia of the right kidney
10	BC	Tubular	E	—	—
11	BC	Tubular	D	—	Cleft lip, hydropelvis, single umbilical artery[b]
12	BC	Type B interruption	F	—	Single umbilical artery[b]
13	BC	Tubular	C_2	Partial anomalous pulmonary venous drainage	Horseshoe kidney

*Ao V, aortic valve; Ao arch, aortic arch; BC, bicuspid; Tubular, tubular hypoplasia; UC, unicuspid.
[a]Type of aortic abnormalities: See Fig. 2.
[b]Absence of right umbilical artery.

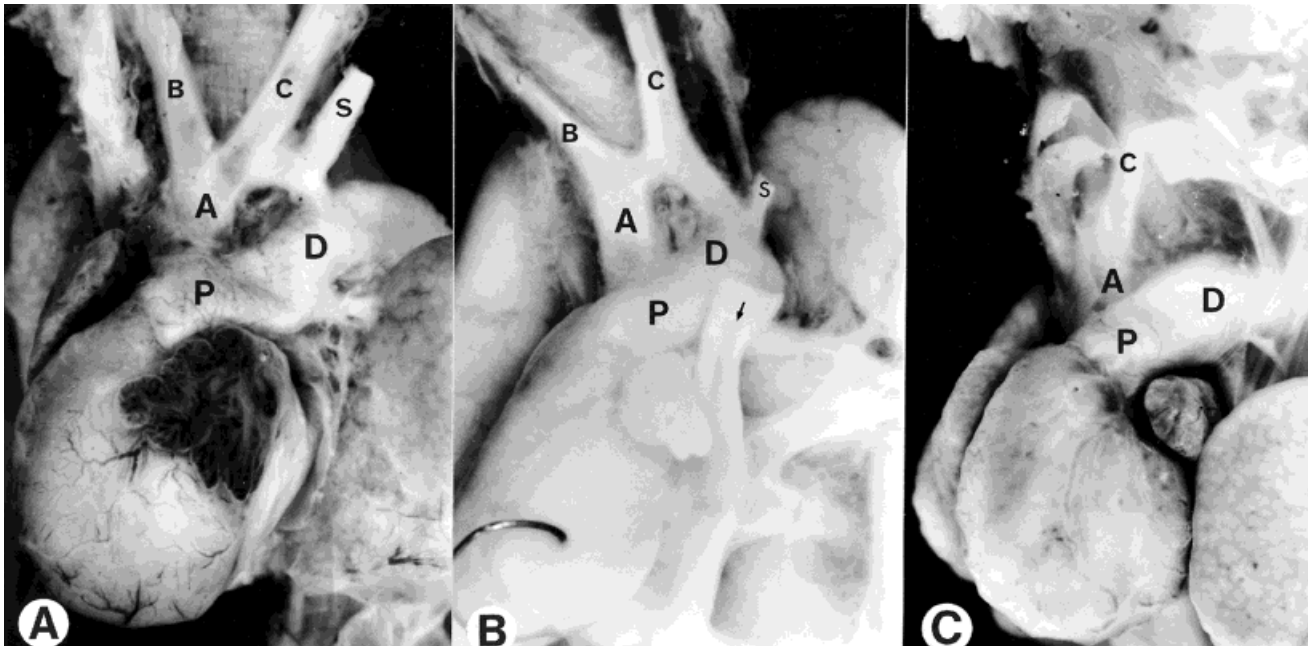

Fig. 4. Photomacrographs showing different types of aortic arch abnormalities in 45,X fetuses. **A:** (Case 13): Tubular hypoplasia between the left common carotid artery and the ductus arteriosus. The aortic arch is stretched slightly. **B:** (Case 3): Marked tubular hypoplasia of the aortic arch with persistent left superior vena cava (arrow) draining into the right atrium through the dilated coronary sinus. **C:** (Case 12): Interruption of the aortic arch after branching of the left common carotid artery. The left subclavian artery is not shown.

every 45,X fetus with cystic hygroma had an abnormal aortic valve. It is remarkable that the aortic valve was also abnormal in fetuses, including a case of trisomy 13, with cystic hygroma. The semilunar valve was completely absent in these cases [Miyabara et al., 1994].

The findings of the left ventricle, aortic valve, ascending aorta and aortic arch suggest a decreased blood flow through the left heart in 45,X fetuses. Experimental treatment of chick embryos to reduce the blood flow to the left heart produced a hypoplastic left heart but it failed to produce a bicuspid aortic valve [Harh, 1973; Sweeney, 1981; Pexieder, personal communication on the work of Dr. Rychter, 1991]. Their evidence should be taken as suggesting that reduced blood flow to the left heart alone does not induce the combined lesion extending from the aortic valve to the aortic arch.

Clark's hypothesis is often cited to explain the cystic hygroma-hypoplastic left heart sequence in UTS with web neck [Clark, 1984]. According to his hypothesis, dilated lymph vessels on the surface of the ascending aorta selectively interfere with the blood flow of the left heart, inducing hypoplastic development. Indeed, a study supported this hypothesis by a finding that dilated vessels were observed around the ascending aorta [Lacro et al., 1988]. The present study showed many dilated vessels not only around the ascending aorta but also around the pulmonary trunk. This finding seems to be inconsistent with the hypothesized selective interference, although it is doubtful whether such dilated vessels in midgestation still manifest an initial lesion around the time of organogenesis.

It is meaningful that type B interruption of the aortic arch is not infrequently observed in DiGeorge anomaly together with bicuspid aortic valve [Moerman et al., 1980; Van Mierop and Kutsche, 1984]. Either type B interruption or coarctation (possibly tubular hypoplasia) between the left carotid artery and the left subclavian artery was observed in children of familial DiGeorge anomaly with 22q11 deletion [Wilson et al., 1991]. The nature of the malformations suggests that the developmental mechanisms in the arch and valve of 45,X embryos are similar to those of DiGeorge anomaly.

It is well known that neural crest cells play an important role in the development of the truncus and aortic arch [Kirby and Waldo, 1990]. The cells usually migrate into the branchial arch and pouch, and further into the aorticopulmonary septum. The semilunar valve is argued to be the destination of their migration through the branchial arch [Takamura et al., 1990]. The cells participate in thymus formation and differentiate into smooth muscle cells in the aortic arch. An ablation experiment of the cranial neural crest in chick embryos clearly showed homologous malformations to DiGeorge anomaly [Nishibatake et al., 1987]. Defects in the neural crest cells are the most likely suspects causing abnormalities from the aortic valve to the aortic arch in 45,X fetuses. Neural crest defect would also explain the finding that only a small number of smooth muscle cells was recognized in the tunica media of the hypoplastic aortic arch. A similar pathogenesis was proposed in the case of coarctation of the aorta and bicuspid aortic valve [Kappetein et al., 1991].

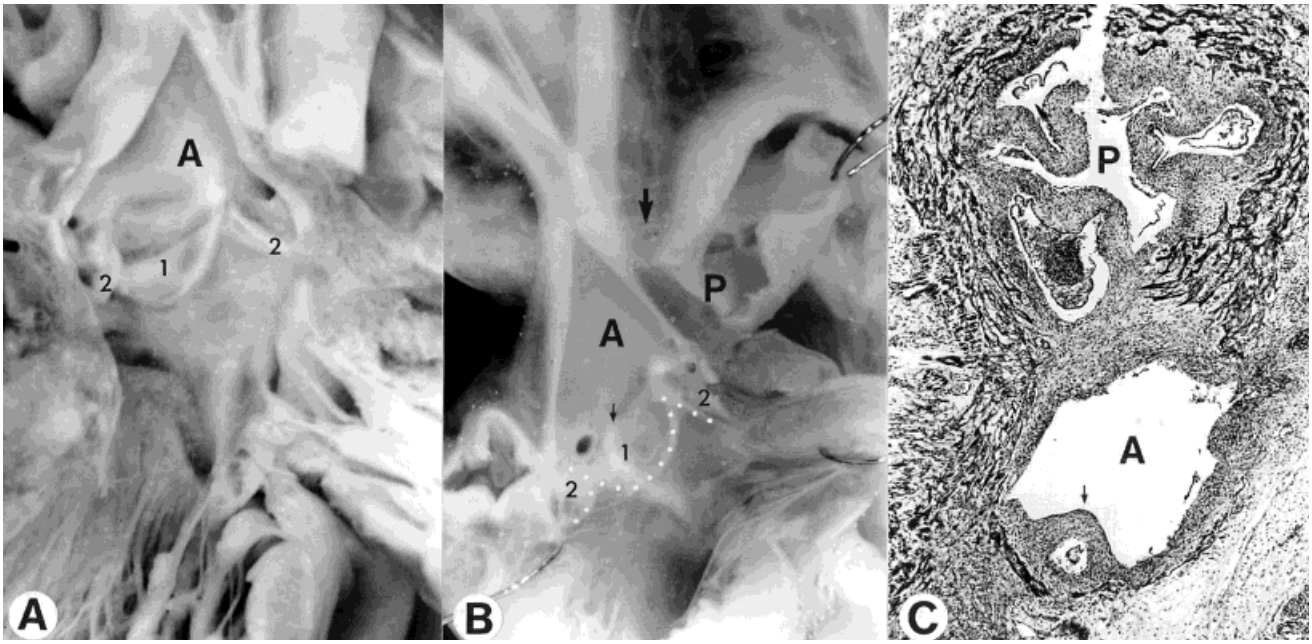

Fig. 5. Different types of abnormal aortic valve in 45,X fetuses. **A:** (Case 11): Bicuspid aortic valve (1 and 2) with equal size. **B:** (Case 12): Bicuspid aortic valve (1 and 2) with unequal size. A raphe (small arrow) formed on the left side of the right coronary ostium is not fused with the semilunar valve 1. **C:** (Case 1): A valve-like tiny tissue (arrow) at the expected site of the semilunar valve in the hypoplastic ascending aorta. ×10.

A histological study further showed abnormal development of the parathyroid gland in 45,X fetuses [Miyabara, 1995]. Only one, possibly lower, parathyroid gland was recognized on the left side, while either two (two cases) or one (two cases), possibly lower, gland on the right side was seen in four 45,X fetuses. This finding indicates hypoplastic development of the fourth branchial pouch in 45,X embryos, explaining the mildly to moderately hypoplastic thymus. The findings in the parathyroid, thymus and aortic arch of 45,X fetuses suggest hypoplastic development of the 4th pharyngeal pouch and the 4th branchial arch including the aortic arch.

It should be noted that the abnormalities of UTS include hypertelorism, ptosis of the eyelids, epicanthus, downwards slanting palpebral fissures, high-arched palate, abnormal mouth, low-set ears, micrognathia, and short neck [Ullrich, 1930; Grumbach and Van Wyk, 1974]. Each of these abnormalities is also observed in the DiGeorge anomaly [Radford et al., 1988], though

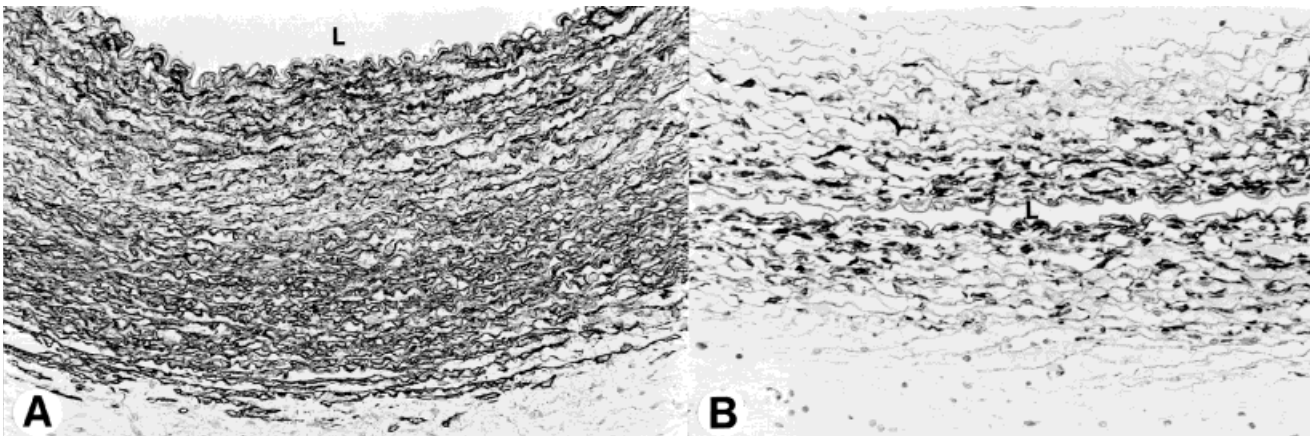

Fig. 6. Photomicrographs of the aortic arch. Smooth muscle cells are demonstrated by an anti-α-smooth muscle actin antibody and elastic fibers are stained by Victoria blue. **A:** (A 21-week-old normal fetus): Note well developed aortic wall. **B:** (Case 7, a 20-week-old 45,X fetus): Markedly reduced numbers of smooth muscle cells and elastic fibers in a thin aortic wall. ×80. L, lumen of the aortic arch.

resultant craniofacial abnormalities are dissimilar between the syndrome and the anomaly. It is also noteworthy that multiple pigmented nevi in UTS [Grumbach and Van Wyk, 1974] are related to a neural crest cell origin. Abnormalities related to the neural crest cells seem to be latent over the face, skin, parathyroid gland, thymus, and cardiovascular system in UTS or 45,X fetuses.

Fetuses of 45,X are more often associated with cervical cystic hygroma than those of other chromosome aberrations. The cystic hygroma is considered to be formed by a dilated cervical lymph sac. A developmental field defect is suspected for the lesions from the nucha to the anterior mediastinum of 45,X fetuses. Abnormal extracellular matrices interfering with migration of cells including the neural crest were hypothesized as the pathogenesis of the phenotype of 45,X fetuses [Miyabara et al., 1989].

Recent molecular genetic studies indicated two homologous genes, RPS4X on the X chromosome and RPS4Y on the Y chromosome, that encode isoforms of ribosomal protein S4 [Fisher et al., 1990]. RPS4X is known to escape X inactivation. A single dose of these genes is suspected to reduce protein synthesis, producing the phenotype typical to UTS. The abnormal morphogenesis in 45,X embryos under this condition remains obscure.

One or a few genes may be involved in the pathogenesis of the lesions from the nucha to the anterior mediastinum of 45,X fetuses. The most plausible candidates are homeobox genes, although the evidence is still fragmented at present. One example in gene-targeted mice is that homozygotes for null mutations of Hox-1.5 showed abnormalities similar to DiGeorge anomaly [Chisaka and Capecchi, 1991]. A special homeobox gene, tinman, was determined to be responsible for the development of cardiac mesoderm in Drosophila [Bodmer, 1993]. In 45,X embryos, certain homeobox genes could play roles in the pathogenesis of cystic hygroma, hypoplastic aortic arch and bicuspid aortic valve as well as hypoplastic heart, and possibly cubitus valgus. Further studies are expected to elucidate the pathogenesis in 45,X abnormalities.

ACKNOWLEDGMENTS

We thank Dr. Kyohko Abe, Kyushu Medical Science Nagasaki Laboratory, Nagasaki, for her valuable advice. The authors are deeply indebted to Mr. Hiroyuki Ideguchi and Mr. Toyoji Tanamach, Pathology Laboratory and Photolaboratory, Saga Medical School, respectively, for their kind technical assistance.

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